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10/500,173	06/24/2004	Katsuhito Takahashi	4439-4022	3299

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
01/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/500,173	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,9-13,18,20,21,23-26,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7,9-13,18,20,21,23-26,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claims 2-5, 8, 14-17, 19, 22, and 27-34 have been cancelled. Claims 1, 6, 9, 20, 21, 35, and 36 have been amended.

Claims 1, 6, 7, 9-13, 18, 20, 21, 23-26, 35, and 36 are pending and under examination.

3. All rejections/objections pertaining to claims 3, 4, 8, 22, and 27-34 are moot because Applicant cancelled the claims in the response filed on 10/15/2007.

Response to Arguments

Specification

4. The specification remains objected to for the reasons of record set forth in the non-final Office Action of 04/21/2006. Applicant's request that the submission of a re-translated version of the specification be deferred is acknowledged, however, the objection is maintained until Applicant submits a retranslated version.

Double Patenting

5. Claims 1, 6, and 7 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/477,797 in view of Martuza (U.S. Patent No. 5,728,379) and Yamamura (Cancer Res 5/2001, 61: 3969-39770) for the reasons of record set forth in the non-final Office action of 06/14/2007 because Applicant did not submit a terminal disclaimer.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The rejection of claim 21 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, is withdrawn in response to Applicant's amendment to the claim filed on 10/15/2007.

7. The rejection of claims 35 and 36 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

8. The rejection of claims 6 and 7 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

9. The rejection of claims 1, 6, 7, 9-13, 18, 20, 21, and 23-26 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

Claim Rejections - 35 USC § 112 - enablement

10. Claims 1, 6, 7, 9-13, 18, 20, 21, and 23-26 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons of record set forth in the prior Office actions. Applicant's arguments filed on 10/15/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the claims, as amended, recite "a region containing a promoter of the human calponin gene comprising the nucleotide sequence shown in SEQ ID NO: 1", and therefore, it is irrelevant that Yamamura et al. do not teach that the sequence between positions 1260 and -219 (i.e., SEQ ID NO: 1) can by itself promote tissue specificity. Applicant argues that, even assuming that one of skill in the art would know that regions other than that defined by SEQ ID NO:1 are important for tissue specificity, the amended claims now include regions other than SEQ ID NO: 1. Therefore, Applicant submits that one of skill in the art could make and use the claimed invention without undue experimentation and that the rejection should be withdrawn.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant claims a vector that is capable of cell-specific expression. The question is not whether one of skill in the art would know how to make a vector comprising the promoter set forth by SEQ ID NO: 1; the question is whether such a vector would work according to the claims, i.e., driving cell-specific expression. The claims, as amended, encompass the full length human calponin promoter and any sub-sequence of the calponin promoter comprising SEQ ID NO: 1 and regions other than SEQ ID NO: 1, i.e., any sub-sequence of SEQ ID NO: 3 comprising SEQ ID NO: 1. The art does not teach, and Applicant did not demonstrate, that a region of the human calponin promoter that is shorter than the full length promoter and comprising SEQ ID NO;1 is sufficient to confer tissue/cell specificity, a feature essential for the claimed invention. Therefore, one of skill in the art would not recognize that the invention would work as claimed.

In conclusion, the specification is only enabling for a cell-specific HSV vector comprising the full length human calponin promoter (i.e., SEQ ID NO: 3) operably linked to an ICP4 gene and a DNA encoding a desired protein.

11. The rejection of claims 1, 3, 4, 6-13, 18, 20, 21, 23-26, 35, and 36 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

Claim Rejections - 35 USC § 112, new matter

12. Claims 1, 6-13, 18, and 20-34 remain rejected under 35 U.S.C. 112, first paragraph, as introducing new matter, for the reasons of record set forth in the non-final Office action of 04/21/2006. Applicant's arguments filed on 10/15/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that, even if the specification does not recite "normal differentiated cells", the limitation of avoiding replication in normal differentiated cells is inherent to the claimed invention because the specification provides an ample number of example wherein only proliferating cells are specifically targeted. Therefore, Applicant argues, the specification provides support for an HSV vector that does not replicate in normal differentiated cells and the rejection should be withdrawn.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

The specification only discloses a vector that does not replicate in "normal adult cells". While it is true that the limitation of "normal differentiated cells" is inherently included in the genus of "normal adult cells", the genus of "adult normal cells" encompasses cells other than "normal differentiated cells". For example the genus encompasses undifferentiated cells such as stem cells found in the adult organism; the specification does not provide any basis for excluding these cells and specifically pick only the normal differentiated cells from the genus of "normal adult cells". The exclusion

of stem cells is not inherently supported by the specification. For these reasons, the rejection is maintained.

13. The rejection of claims 1, 6, 7, 9-13, 18, and 20, 21, 23-26, 35, and 36 under 35 U.S.C. 112, first paragraph, as introducing new matter, is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

Claim Rejections - 35 USC § 103

14. The rejection of claims 1, 6, and 7 under 35 U.S.C. 103(a) as being unpatentable over Martuza (U.S. Patent No. 5,728,379), in view of both Yamamura (Cancer Res 5/2001, 61: 3969-3977) and Chung et al. (J Virol, 1999, 73: 7556-7564) is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

15. The rejection of claims 1, 6, 7, 16-18, 20, 25, and 26 under 35 U.S.C. 103(a) as being unpatentable over Chung et al., in view of Yamamura et al. is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

16. The rejection of claims 1, 6, 7, 16-18, 20, and 23-26 under 35 U.S.C. 103(a) as being unpatentable over Chung et al. taken with Yamamura et al., in further view of Tjuvajev et al. (Cancer Res, 1998, 58: 4333-4341, Abstract) is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

17. The rejection of claims 1, 6, 7, 18, 20, 21, 25, and 26 under 35 U.S.C. 103(a) as being unpatentable over Chung et al., in view of each Yamamura et al., Van Meir et al. (PGPUB 2005/0074430, of record), and Miyatake et al. (Stroke, 1999, 30: 2431-2439) is withdrawn in response to Applicant's amendments to the claims filed on 10/15/2007.

New Rejections

Claim Rejections - 35 USC § 112, enablement

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a cell-specific HSV vector by using the full length human calponin promoter, does not reasonably provide enablement for a method of producing a cell-specific HSV vector by using a promoter of the human calponin gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Specifically, the specification fails to provide support for a promoter having a sequence which is shorter than the full length human calponin promoter, wherein the promoter that imparts cell specificity.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

Applicant claims a vector that is capable of cell-specific expression, wherein the vector comprises a promoter of the human calponin gene. The claims, as amended, encompass the full length human calponin promoter (disclosed in the specification as being set forth by SEQ ID NO: 3), the minimal calponin promoter set forth by SEQ ID NO: 1, and any other sub-sequence comprising the minimal calponin promoter (for example the sub-sequence disclosed in the specification as being set forth by SEQ ID NO: 2). Although the minimal promoter and the sub-sequences comprising the minimal promoter are portions of the full length calponin promoter, there has been no showing that they are sufficient to grant tissue specificity. It is noted that, although the art teaches that the minimal calponin promoter is sufficient for inducing calponin gene transcription in HOS (osteosarcoma) and HMC (mesangial) cell lines, the art does not teach that this region can by itself promote tissue specificity (see for example Yamamura et al., Cancer Res, 2001, 61: 3969-3977, of record). There is a difference between induction of transcription and tissue/cell specificity. Absent evidence to the

contrary, the minimal promoter can perform equally well in different tissues/cells (i.e., does not confer cell specificity) and it is possible that additional regions contained only in the full length calponin promoter are required to confer tissue/cell specificity. Yamamura et al. teach that the minimal promoter includes consensus-binding sites for Sox and GATA-1 transcription factors. However, these factors are not cell-specific, as they can control transcription from a variety of promoters in different cell and tissue types. Yamamura et al. do not teach that Sox and GATA-1 are implicated in conferring tissue/cell specificity for the calponin promoter. The art does not teach, and Applicant did not demonstrate, that the minimal promoter by itself or sub-sequences comprising the minimal promoter are sufficient to confer tissue/cell specificity; the art and the specification only teach the full length promoter as having tissue specificity. Therefore, one of skill in the art would not recognize that regions shorter than the full length calponin promoter could confer cell specificity. In full support of this, the specification at the paragraph bridging pages 34 and 35 clearly identifies the full length promoter as the required minimal expression regulatory region. Thus, by Applicant's own admission, the full length promoter is the minimal domain required to achieve the tissue specificity granted. The specification offers no evidence that either the minimal promoter or any other subsequence comprising the minimal promoter could act in the tissue specific manner desired. There is no guidance regarding any structural or sequence requirements or functional domains required to impart cell-specific activity. Therefore, neither the art nor the specification teach that a region of the human calponin promoter that is shorter than the full length promoter is sufficient to confer tissue/cell specificity, a

feature essential for the claimed invention. Therefore, one of skill in the art would not recognize that the invention would work as claimed.

In conclusion, the specification is only enabling for a method of producing a cell-specific HSV vector by using the full length human calponin promoter.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 1, 6, 7, 18, 20, 21, 25, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 5,728,379, of record), in view of both Yamamura et al. (Cancer Res 5/2001, 61: 3969-3977, of record) and Chung et al. (J Virol, 1999, 73: 7556-7564, of record).

Martuza et al. teach an HSV vector, wherein a cell-specific promoter drives the expression of ICP4, wherein the HSV vector does not replicate in the normal differentiated cells, wherein the HSV vector contains the intact TK gene, wherein the vector comprises tissue-specific enhancers upstream of the tissue-specific promoter, and wherein the vector expresses therapeutic factors in a tissue-specific manner, i.e., the vector comprises a DNA encoding a desired protein wherein the DNA is downstream of the ICP4 gene and under the control of the tissue-specific promoter; the cell-specific promoters are derived from genes that are highly expressed in tumor cells

(claims 1 and 6) (column 4, lines 40-59, Figure 1 and its Brief description at column 6, lines 42-45, column 4, lines 30-67, column 11, lines 4-16, column 25, lines 39-56, claims 1-3, 12, and 13). Therefore, Martuza et al. also teach a method for expression of a gene in tumor cells by using an HVS vector, wherein the HSV vector does not replicate in normal differentiated cells (claims 20 and 25). In addition to the above, Martuza et al. teach the use of ganciclovir to suppress the replication of their HSV vector, i.e., they teach a method for suppressing the expression of the DNA encoding the desired protein (claim 21) (column 7, lines 20-35, column 25, lines 51-55, column 33, lines 48-64). Martuza et al. teach their HSV vector as comprising a disrupted ribonucleotide reductase (RR) gene, wherein the vector is obtained by disruption of the RR gene via insertion of the *lacZ* gene into the RR locus by homologous recombination, co-transfecting the *lacZ*-containing fragment with a viral DNA into Vero cells (i.e., cells which do not express ICP4 and which contains transcription factors that activate the calponin promoter), and purifying clones by limiting dilution (claims 1, 35, and 36) (Fig. 4 and 5, column 5, lines 1-9 and 39-45, column 21, lines 40-60, Example 1). Martuza et al. teach that RR disruption is essential for therapeutic vectors, wherein RR disruption results in increased sensitivity to acyclovir and ganciclovir and wherein the RR-disrupted vectors are less likely to replicate in normal differentiated cells (column 22, lines 1-3 and 24-40, column 25, lines 57-62).

Although Martuza et al. teach that the DNA fragment comprising ICP4 operably linked the tissue specific promoter can be inserted in any location of the HSV genome by homologous recombination, they do not specifically teach inserting into the

ribonucleotide reductase locus (claims 1 and 35). However, this is not innovative over the prior art. For instance, Chung et al. teach insertion of a DNA comprising a tissue specific promoter operably linked to a gene essential for HSV virulence into the RR locus (p. 7558, Fig. 1, p. 7557, column 1, second paragraph and column 2, *Results*); and Martuza et al. teach that the DNA fragment comprising ICP4 operably linked the tissue specific promoter can be inserted in any location of the HSV genome (column 25, lines 50-55). It would have been obvious to one of skill in the art, at the time the invention was made, to insert the DNA fragment comprising ICP4 gene operably linked the tissue specific promoter into the RR locus, to achieve the predictable result of obtaining a vector suitable for gene therapy, which vector does not replicate in the normal differentiated cells and which vector exhibits increased sensitivity to acyclovir and ganciclovir (see *KSR International Co. v. Teleflex Inc.,* 550 U.S., 82 USPQ2d 1385, 2007). The limitation of cloning without agarose overlay (claims 1 and 35) is again not innovative over the prior art; the patentability of the composition does not depend on the method of obtaining it (see MPEP 2113 [R-1]). The instant end product (i.e., the HSV vector) is identical to the end product taught by the combined teachings above, regardless of whether cloning takes place with or without agarose overlay. Applicant did not provide any evidence that cloning in the absence of agarose overlay results in an HSV vector which is structurally different from the HSV vector taught by the cited prior art.

Although Martuza et al. teach a cell-specific promoter and an enhancer, they do not specifically teach the full length calponin promoter or the 4F2 enhancer (claims 1

and 7). Yamamura et al. teach the calponin promoter driving the expression of the ICP4 gene and the 4F2 enhancer, wherein the 4F2 enhancer is integrated upstream to the calponin promoter and wherein the 4F2 enhancer further upregulates ICP4expression (p. 3970, column 1, fourth full paragraph and Figure 1A and 1B, p. 3972, column 1, first paragraph). Yamamura et al. also teach that calponin is highly expressed in a variety of human soft tissue and bone tumors (Abstract, p. 3969, column 2, p. 3976, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the HSV vector of Martuza et al. by using the calponin promoter together with the 4F2 enhancer, with a reasonable expectation of success. One of skill in the art would have been motivated to use the calponin promoter in order to target therapeutics to the human soft and bone tumor cells. One of skill in the art would have been motivated to use the 4F2 enhancer becauseYamamura et al. teach that insertion of the 4F2 enhancer upstream of the calponin promoter increases the transcriptional activity of the calponin promoter (p. 3972, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a vector because the art teaches that such vectors can be successfully made and because Martuza et al. teach that promoters derived from genes highly expressed in tumor cells can be successfully used to specifically drive vector replication in tumor cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

22. Claims 1, 6, 7, 9-13, 18, 20, 21, 25, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with both Yamamura et al. and Chung et al., in further view of Van Meir et al. (PGPUB 2005/0074430, of record).

The teachings of Martuza et al., Yamamura et al., and Chung et al. are applied as above for claims 1, 6, 7, 18, 20, 21, 25, 35, and 36. Although Martuza et al., Yamamura et al. and Chung et al. teach their vector as comprising a DNA encoding a desired protein, they do not specifically teach a protein that induces apoptosis (claim 10) or a protein that inhibits apoptosis (claims 11-13), nor do they teach linking the DNA via an IRES (claim 9). Van Meir et al. teach therapeutic HSV vectors comprising a DNA encoding a protein which promote apoptosis (claim 10) or a protein which inhibits angiogenesis (claims 11-13), wherein the DNA is linked to an HIV replication gene via an IRES (claim 9) (p. 1, paragraph 0007, p. 3, paragraphs 0020 and 0023, p. 6, paragraph 0056, p. 7, paragraph 0074, p. 8, paragraphs 0080-0085 and 0089). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector of Martuza et al., Yamamura et al. and Chung et al. by using IRES to link a DNA encoding a protein that promotes apoptosis or inhibits angiogenesis to the ICP4 gene, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain a vector suitable for cancer therapy, wherein the vector is capable of killing tumor cells by promoting tumor cell apoptosis or by inhibiting tumor angiogenesis. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a vector because the art teaches that such vectors can be successfully made and used.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

23. Claims 1, 6, 7, 18, 20, 21, 25, 26, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with both Yamamura et al. and Chung et al., in further view of Miyatake et al. (Stroke, 1999, 30: 2431-2439, of record).

The teachings of Martuza et al., Yamamura et al., and Chung et al. are applied as above for claims 1, 6, 7, 18, 20, 21, 25, 35, and 36. Martuza et al., Yamamura et al., and Chung et al. do not teach therapy by targeting the virus to proliferating smooth muscle cells (claims 18 and 26). However, this are not innovative over the prior art. For example, the art teaches using tissue specific replication competent HSV vectors to inhibit smooth muscle cell proliferation (see Miyatake et al., the whole paper). One of skill in the art would have known, would have been motivated, and would have been expected to have a reasonable expectation of success in using the vector taught by Martuza et al., Yamamura et al., and Chung et al. (i.e., replication competent and, since calponin is highly expressed in proliferating smooth muscle cells, specific for proliferating smooth muscle cells) to treat disorders associated with smooth muscle cell proliferation, because the art teaches the usefulness of using such vectors to treat disorders associated with cell proliferation, including those characterized by smooth muscle proliferation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

24. Claims 1, 6, 7, 18, 20, 21, 23-25, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with both Yamamura et al. and Chung et al., in further view of Tjuvajev et al. (Cancer Res, 1998, 58: 4333-4341, Abstract, of record).

The teachings of Martuza et al., Yamamura et al., and Chung et al. are applied as above for claims 1, 6, 7, 18, 20, 21, 25, 35, and 36. Martuza et al., Yamamura et al., and Chung et al. do not teach detecting the *in vivo* distribution of the vector by determining tk activity using positron emission tomography (PET) and FIAU labeled with ^{124}I (claims 23 and 24). Tjuvajev et al. teach the noninvasive imaging of *tk* gene transfer and expression by PET and FIAU labeled with ^{124}I. It would have been obvious, to one of skill in the art, at the time the invention was made, to monitor the distribution and expression of the vector taught by Martuza et al., Yamamura et al., and Chung et al. by using PET and FIAU labeled with ^{124}I, with a reasonable expectation of success. The motivation to do so is provided by Tjuvajev et al., who teach their method as useful for providing the information necessary for monitoring clinical gene therapy. One of skill in the art would have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of the method to monitor transgene expression.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

Joe Woitach
AU1633